

Ethical Questions on the Use of Magnetic Field Reports

Results from National Toxicology Program draft reports on carcinogenesis and promotion of 60-Hz magnetic fields (1,2) are a mixed bag of apparent effects in some cases and no effects in other cases. The studies were carried out, apparently, with the intent to provide information that can be used in making health policy for humans. I contend that these studies cannot be used for this purpose because of two implicit assumptions that were made when the studies were being designed.

First, it was assumed that the relevant magnetic field parameter for inducing biological effects is a pure 60-Hz sine-wave, and such was used. But the public is exposed to something very different, as the authors admit (1):

While power line magnetic field exposures are predominantly sine-wave fields, residential and occupational exposures may include square waves, sawtooth waves, and other wave forms. Harmonics (120 Hz, 180 Hz, etc.) may also be found. Further, as appliances are switched on and off, spikes or transients in fields may occur. It is not feasible to evaluate all possible variables in large animal studies. Therefore, this study used linearly polarized, pure sine-wave exposures at 60 Hz, with the fields turned on when the sine wave was at zero amplitude and gradually increased over seven to nine cycles (between 0.11 and 0.15 seconds) to full intensity, and similarly gradually decreased to avoid transients. The NIEHS studies evaluate the predominant component (60-Hz sine-wave magnetic fields) without all the complexities of the exposures that occur in residential and occupational settings.

Biological theory, as well as substantial published data, indicates that the field characteristics which people are actually exposed to, and which the authors eliminated from their experiments, are the effective agents (3). Thus, if one wants to use the results of these studies in setting health policy for people exposed to power line fields, one must first prove that a pure sine-wave field is the relevant parameter for inducing biological effects.

The second implicit assumption made by the authors was that magnetic fields are an alien substance, such as arsenic, etc. Thus, they set up the experiments using a toxicology model—in a dose-response format. In fact, electrical and magnetic fields are not alien substances; rather, they are fundamental in the functioning of living organisms. I have addressed this matter in detail in several publications (3,4). Thus, if one wants to use the results of these studies in setting health policy for people exposed to power line fields, one must first prove that a toxicology model is appropriate.

Although the technology in these experiments may be fine, it would not be ethical to use the results in the formulation of health policy for the human population without

first proving that the implicit assumptions that were made are true. These comments also apply to other recent studies, such as the study by Mandeville et al. (5).

Allan H. Frey
Randomline, Inc.
Potomac, Maryland

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2. NTP. Studies of Magnetic Field Promotion (DMBA Initiation) in Sprague-Dawley Rats (Gavage/Whole-Body Exposure Studies)-Draft. Research Triangle Park, NC: National Toxicology Program, 1998. <http://ehis.niehs.nih.gov/ntp/docs/tr489/489full.pdf> [cited February 1998].
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Response: Magnetic Field Reports

The logic of Allan Frey's first criticism ("First, it was assumed that the relevant magnetic field parameter for inducing biological effects....") is unclear. By citing remarks of the authors (1), he is acknowledging that the predominant component of environmental fields is the 60-Hz component (60 Hz in the United States and 50 Hz in Europe), yet he is being critical of its use as the candidate exposure parameter in the toxicology and carcinogenesis studies, which is puzzling. His reasons for dismissing the 60-Hz component as the active agent are "Biological theory as well as substantial published data...." indicate that other attributes of the magnetic field are the "effective agent," and he cites a reference of his own (2) in support of his position. Apparently Frey has not read the breakout group report from the first RAPID Program Science Review Symposium on theoretical mechanisms and *in vitro* findings (3), which considered mechanism theories for EMF biological effects. The report (3), reflecting the views of experts in 1997, indicates that the biological effects that have been reported in the literature are "not expected based on known biophysical mechanisms." Therefore, it is not clear what "biological theory" Frey is referring to. Frey suggests that "properly tuned" magnetic fields should be used for exposure purposes (4). The main magnetic fields of interest have been those of power frequencies; however, in the EMF

RAPID program, other magnetic field frequencies are being considered.

In regard to the "substantial published data" that supports Allan Frey's first criticism, he has failed to note that there has been no independent replication of the biological effects reported in the archival literature. The four EMF Regional Exposure Facilities (at the Food and Drug Administration in Rockville, MD; the National Institute for Occupational Safety and Health (NIOSH) in Cincinnati, OH; the Oak Ridge National Laboratories in Oak Ridge, TN; and the Pacific Northwest Laboratories, in Richland, WA) supported by the EMF RAPID program and the Department of Energy (DOE), where all studies are done in a blind fashion including sham/sham controls, have failed to replicate a single *in vitro* effect after 3 years of effort. Only recently have there been reports of replication of an *in vitro* study (conducted elsewhere and yet to be published). The failure in the United States (5) to replicate the cancer promotion results that were first observed in Germany using "pure sine-wave" power frequency magnetic fields is a recent example in which the replication effort was unsuccessful. Because the original promotion study employed pure sine-wave magnetic fields and reported adverse biological effects, the same purely sinusoidal fields had to be used in the replication effort. Why Frey is critical of the use of sine-wave fields in the promotion replication study is unclear.

Frey's view that "one must first prove that a pure sine-wave field is the relevant parameter for inducing biological effects" is better directed at the other candidate exposure parameters. For example, transients (spikes) in the magnetic field have been suggested as a candidate exposure parameter. In 1991, when the protocols for the toxicology study were being developed, there were no published data or theory regarding transients. It was not until September 1994 at the DOE/NIOSH workshop on EMF exposure assessment that fast transients were suggested as a candidate exposure parameter. In considering other candidate exposure parameters, the NIEHS, through the EMF RAPID program, supported an evaluation of the third and fifth harmonic, transients, and intermittent field exposures in rats using pineal and serum nocturnal melatonin levels, pineal serotonin *N*-acetyltransferase activity, and ornithine decarboxylase levels in various tissues as parameters of a biological effect. These studies have been completed and the results were presented at the third Science Review Symposia, held in Phoenix, Arizona 5–9 April 1998.

Gary A Boorman
National Institute of Environmental
Health Sciences
Research Triangle Park, NC

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The Importance of Protocol Design and Data Reporting to Research on Endocrine Disruption

Several recent articles have discussed the doubts expressed by some scientists regarding the validity of endocrine disruption studies conducted by industrial scientists or sponsored by the chemical industry (1–3). The last of these articles (3) recounted personal attacks made on the integrity of Stephen Safe of Texas A&M University.

It is in the nature of any new branch of toxicology that, at least initially, adverse effects may be discovered for chemicals by those academic laboratories working in the new area. The chemical industry is then left to confirm and extend the findings of others. Such confirmatory studies are usually necessary because the initial publications often describe the results of limited or unreplicated experiments (4). The articles mentioned above (1–3) concerned the prospect that repeat studies conducted by or sponsored by the chemical industry are designed in order not to confirm the original observation. We wish to discuss the complementary concern that many new findings in this area are either inadequately described or are based on data derived using inadequate test protocols. This makes it difficult to conduct faithful repeat experiments, however well-motivated the responsible scientists are.

We recently decided to confirm and extend adverse endocrine toxicities reported for nonylphenol (NP) and bisphenol-A (BPA). For both of these chemicals, we experienced problems when attempting to design repeat experiments due to inadequacies of the original publications. These inadequacies may seem to be relatively minor, but when the

outcomes of the repeat experiments are likely to be challenged, they become important.

Three influential papers using the Noble rat have been published by Colerangle and Roy over the past 4 years (5–7). The papers in question report the results of implanting the estrogens estrone, diethylstilbestrol (DES), NP, or BPA into Noble rats and monitoring the consequent changes in cell growth in the mammary gland. Either pellets or mini-pumps were used to deliver the test chemicals over 11 days. In each case growth of the mammary gland was reported. A significant aspect of these results is that estrogenic effects were found for NP and BPA at much lower dose levels than would have been expected based on the results of earlier studies (8–11), in particular, rat uterotrophic assays conducted using three daily administrations of the test chemicals. To resolve the uncertainties created by this apparent difference in assay sensitivities, we embarked on full repeats of the DES and NP Noble rat mammary gland assays (5–7). We also conducted rat uterotrophic assays utilizing the dosing protocol used by Colerangle and Roy [the test compound administered over 11 days via subcutaneously implanted mini-pumps (5–7)] and multiple strains of rats, including the Noble strain.

The following inadequacies of the three published studies in Noble rats have complicated their interpretation and the design of our own studies (5–7).

In the first study (5), DES was administered over 11 days as a subcutaneously implanted pellet. Cell labeling indices and growth fractions of mammary gland cells were determined using the methods of Foley et al. (12). DES was reported to increase the labeling index from 11% (controls) to 71%. Recalculation (12) of these indices from the primary data presented (5) gave values of 11% and 21% for controls and DES, respectively. Likewise, the growth fractions were reported to be 21% for controls and 158% for the DES animals; recalculation (12) from the primary data presented (5) gave values of 21% and 47%, respectively. The estrone figures were also in error. These errors, which have not been formally corrected by the authors, make it difficult to be certain of the magnitude of the effects expected in our repeat experiments. Subsequent data from these authors (6,7) appear to have been correctly calculated based on cell number estimates derived from the bar charts presented.

In the second and third papers (6,7), the activities of NP and BPA in the mammary gland of Noble rats were compared to that of DES. DES was shown as a positive control agent in both of these papers, and in each case the test data were identical to those reported to the original study (5), including use of the incorrect labeling indices and

growth fractions. The wrong impression was thereby given that the DES study had been replicated three times. Further, in the BPA paper (7), the DES is described as being administered via a mini-pump, whereas in the initial paper (5) it is reported to have been given as a pellet. No experimental details were provided for the administration of DES in the NP paper (6). Thus, after three separate publications, the test data for DES have apparently yet to be replicated.

Despite being published separately and a year apart, the vehicle control data for the NP (6) and the BPA (7) studies are the same in each paper and different from those in the original study (5). Either the data for NP and BPA were derived from a single study that was then published in two isolated parts or a vehicle control group was absent from one of the two studies (6,7). This created an unacceptable level of uncertainty.

Thus, while attempting to repeat these significant new findings in the Noble rat, we were presented with uncertainties in the original papers that could have been regarded as intentional had they occurred in our own (industrial) studies.

Nagel et al. (13) reported that BPA increased the weight of the prostate gland in mature CF-1 mice exposed *in utero*. In a subsequent paper from the same laboratory, vom Saal et al. (14) reported the induction of similar effects by DES. When designing a repeat of the CF-1 mouse experiment with BPA, we decided to include DES as a positive control chemical, despite the absence of such a control in the original BPA study (13). However, we were presented with a problem: the BPA animals described by Nagel et al. (13) were terminated at 6 months and the DES animals described by vom Saal et al. (14) were terminated at 8 months. No explanation for this difference in test protocol was given. It was therefore impossible to mount a faithful concurrent report of the BPA and DES experiments; thus, we decided to terminate both of our groups at 6 months. However, that means that we will not have faithfully repeated the original study on DES.

Another aspect of the study by Nagel et al. (13) caused us concern. In that study, two control groups were used: a vehicle control group and a group of animals that were not handled throughout the study. It was stated (13) that these two control groups gave similar data (not shown) and that they were therefore combined into a single, larger control group and used as such for the subsequent statistical analysis of the BPA test data. That represents bad statistical practice. We decided to include two such control groups in our own experiment and to maintain their separate identities during the statistical analysis of our data. Each of these small changes in